Annals of Academy of Romanian Scientists
Online edition *Series: Medical Sciences*
ISSN 2285-4150 Volume 1, Number 1/2010

OUR EXPERIENCE IN TREATMENT OF HAEMOPHILIC ARTHROPATY

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Abstract. *Hemophilia is a hereditary disease due to a defect of chromosome X, which lead to impaired production of coagulation factor VIII in hemophilia A (85% of cases) and factor IX in hemophilia B. distinguish three types of severity: mild with a poor concentration factor greater than 5% of normal values, an average of a concentration between 1 and 5% and a severe, with more than half of cases of hemophilia, with a concentration of factor VIII or IX less than 1% of normal. Hemorrhages in muscles and joints occur spontaneously in severe form, running a minor injury in the moderate and only after a major injury or surgery in mild forms.*
Chronic arthropathy is the principal manifestation of severe and moderate hemophilia.
Elective surgery in patients with classic hemophilia (factor VIII deficiency) and hemophilia B or Christmas disease (factor IX deficiency), became possible and feasible by the availability of concentrated factor VIII and IX. 75 operations was performed.
Synovectomy may be done by open synovectomy or arthroscopic synovectomy. With the increasing use of arthroscopic synovectomy, surgeon should reconsider his decision when choosing between this procedure, open synovectomy or non-surgical synovectomy (synoviorthesis). Ankle, shoulder and elbow arthrodesis has been satisfactory on small series of patients with hemophilia.
With substitute treatment and a correct surgical indication, surgery in haemophilic patients can be performed with acceptable risk and good results.

Keywords: haemophilic arthropaty, synovectomy, hemophilia, knee arthroplasty, hip arthroplasty, musculoskeletal manifestations.

1. Introduction

Hemophilia is a hereditary disease due to a defect of chromosome X, which lead to impaired production of coagulation factor VIII in hemophilia A (85% of cases) and factor IX in hemophilia B. distinguish three types of severity: mild with a poor concentration factor greater than 5% of normal values, an average of a concentration between 1 and 5% and a severe, with more than half of cases of

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hemophilia, with a concentration of factor VIII or IX less than 1% of normal. Hemorrhages in muscles and joints occur spontaneously in severe form, running a minor injury in the moderate and only after a major injury or surgery in mild forms.[1]
Chronic arthropathy is the principal manifestation of severe and moderate hemophilia.
Joint damage cycle is: recurrent haemarthrosis → synovial hypertrophy → chronic synovitis → cartilage damage → incapacitating chronic arthropathy.
The evolution of hemophilic arthropathy is almost always from haemarthrosis to chronic synovitis and extensive erosion of the articular surface and, ultimately, the final stage of joint destruction - chronic hemophilic arthropathy. End stage of arthropathy is complicated by severe limitation of joint range of motion secondary to the arthrofibrosis due to the replacement of the hypertrophic synovitis with a dense fibrosis. Severe contractures, angular deformation and loss of bone substance due to mechanical abrasion and bony cysts are common.[8]
Patients with severe hemophilia have haemarthrosis especially in knee, elbow and ankle with appearance of hemophilic arthropaty. Knee is most commonly affected (30%) followed by elbow (25%), ankle (15%), hip (5%) and other joints (< 2.5%). Arthrosis changes are seen in approximately 90% of affected joints even in moderate forms of the disease. Evolution of haemophilic arthropaty depends on patient age with a maximum deterioration in the second decade.

Clinical manifestations

Bleeding is a major symptom of this disease and is generally produced by a minimal trauma. Intramuscular hematoma, also announced by pain and the swelling, will expose to two types of complications: tendinous retraction and compression. Hemarthrosis is the most common complication of haemophilia, occurring in two thirds of cases. The origin of haemarthrosis is synovial tissue. Chronic arthropaty. Restitution of the joint function will be always complete after the first haemarthrosis; unfortunately, it always reoccurs and will progress at the time of adolescence or adult age to the stage of chronic arthropaty. (**Chart1**)

Early	Erosion of cartilage and deterioration of trabecular structure with increased decalcification
Moderate	Juxtaarticulare cysts, epiphyseal enlargement, accelerated growth, deformation of patella
Severe	Complete destruction of joint surfaces

Chart1. Classification of hemophilic arthropathy (by Jordan).

Stage	
0	Normal joint
1	Inflammation of soft tissues
2	Osteopenia and excessive growth of epiphysis which probably reflects hyperemia
3	Changes in bone contour (intercondillary notch widening, flattening of patella curves and femoral condyle, forming cysts subchondral)
4	Intra-articular space narrowing indicating erosion of cartilage
5	Substantial disruption if the joint

Chart 2. Classification of hemophilic arthropathy by Arnold and Hilgartner.

Imagistic aspects of haemophilic arthropathy

Particularly in adult patients, there is a good statistical correlation between subjective symptoms, scores of physical examination and the X-rays.

Imaging investigations have the merit of:

- Objective evaluation of the ostheoarticular status;
- Provide monitoring parameters, under which it can be established time related dynamics of the observed alterations;
- Provide criteria for sensitivity (MRI) or gravity (DXA) for ostheoarticular evaluation.

Radiological aspects of haemophilia artropathy

Reveals generalized osteopenia and osteoporosis, increased sinovial density, epiphyseal enlargement compared with contralateral joint, joint space narrowing, articular surface irregularity, cystic lesions in the subchondral region, widening and deepening of the intercondylar fossa, subchondral osteosclerosis, incongruent joints, growth of secondary epiphyseal ossification centers , erosion of joint edges and Harris lines.

A wider intercondylar fossa is characteristic of haemophilia after haemarthrosis recurrence. It can also appear in the elbow a radial head enlargement and widening of trochlea. [1]

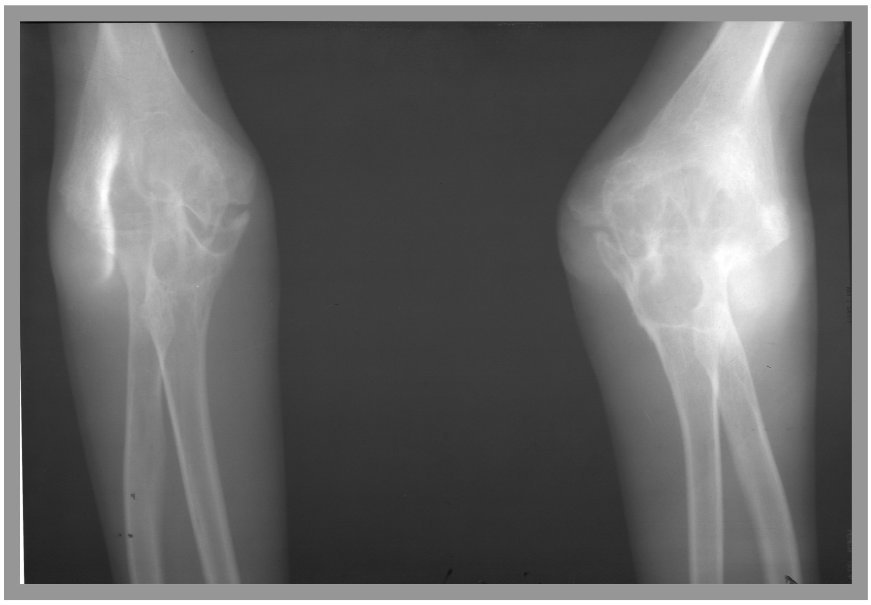

Figure 1. Bilateral chronic haemophiliac arthropathy of the elbow. Enlargement and deformation of epiphysis, disappearance of joint space.

Aspects of the exploration by nuclear magnetic resonance

If radiography will be limited to give only information about bone changes, magnetic resonance imaging provides information on synovial and cartilage. It has high sensitivity in detecting early changes of haemophilic arthropathy. An important aspect is that MRI can be the basis of the indications for prophylaxis, or can recommend the sinovectomy.

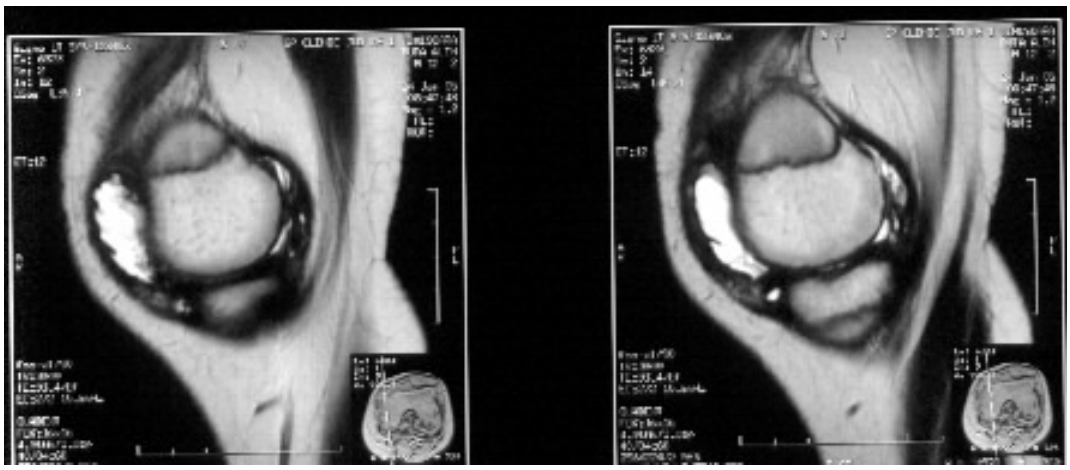

Figure 2. Significant retro patellar haemarthrosis.

Osteodensitometry
In terms of chronic artropathic hemophilia, an account of the factors of structural changes predisposes to bone fractures. In these conditions it is noteworthy role in screening patients with hemophilia, to detect early changes in bone density.

General measures of treatment
Elective surgery in patients with classic hemophilia (factor VIII deficiency) and hemophilia B or Christmas disease (factor IX deficiency), became possible and feasible by the availability of concentrated factor VIII and IX. In the past it was done only saving surgery, and mortality was high. Postoperative hematoma with large clots and infection were common. However catastrophic complications can be minimized by controlling only expert clotting mechanism, and therefore surgery in hemophiliac not be taken at random. Unloading machinery property, elastic imobilization, orthotics can be used together with physical therapy to protect the joints or to treat soft tissue contracture. These measures may be as important as hematological treatment to avoid surgery.

Treatment involves two distinct objectives:
1) *stop the bleeding* and 2) *maintaining hemostasis until healing*.
In addition to the substitute therapy, hemostatic conditions must be improved by local treatment measures. These may be:
Direct: Prolonged compression at the bleeding point, strict immobilization of the region, discharge of extravasated blood and clots.
Indirect: fight against secondary inflammatory phenomena due to corticosteroids and, in case of infectious risk, use of antibiotics, and physiological blockage of fibrinolytic process by inhibitors of fibrinolysis.

Substitution
The most commonly used method today is recombinant factor VIII or factor VIII antibody purified by monoclonal antibodies.
A summary of how to use substitution or surgical bleeding situations is presented in chart 3.
After guides Boston Hemophilia Center, 2/98, B. Ewenstein, + represents the ”Classic” answer of 1UI = 2% increase.

	Haemophilia A		Haemophilia B		
Location	Initial dose (U/kg)	Mantainance dose (U/kg)	Initial dose (U/kg)	Mantainance dose (U/kg)	Desired factor concentration
Acute haemarthrosis					
Early Late	15-30+ 25-50+	Rarely necessary 25q12ore	20 40-80+	Rarely necessary 20-25q24 ore	Early (3 hours of onset): increase concentration to 25-30% repeat as needed Late: increase the concentration 50-100%
Intramuscular haemorrhage	25-50+	25q12hour, often for several days	very mild or moderate: 20-40 Severe: 80	30q12 hours often for several days	Major: thigh, leg, forearm, hip, increase concentration at 100%, maintain a few days-few weeks, then 30-50% for a further period Minor: other sites, superficial bleeding increases factor to 50%, usually for 2-3 days.
Major surgery or trauma	50	25q12ore or 25 followed by continuous iv infusion 3.4 IU/kg/h	80	40q24 hours or loading dose and continuous iv infusion	Initially 100%, 50% during early convalescence, 30% in the late one

Chart 3. Substitution usage in bleeding or during surgery

Prophylaxis with gah

This approach seeks to maintain the level of factor VIII in the range of 1-5% on an ongoing basis. The administration of factor VIII is three times a week and the factor IX twice a week.

This treatment is reserved for severe forms of disease, in part because it is enormously expensive, and maintaining a continuous venous access without infection can be problematic.[5]

Conservative treatment

- Substitute treatment;
- Physiotherapy, NSAIDs and pain treatment;
- Synovectomie chemical or radiation (synoviorthesis);
- Intra-articular injections - cortisone or hyaluronic acid;
- Avoid first haemarthrosis.

Analgesic Treatment

Patient-controlled analgesia is the optimal form of analgesia, given that these patients have a low tolerance to pain. There is usually a high tolerance to opiates in their case being recommended increased attention to management because they are addictive.

Analgesics should be administered in high quantities, the nececesar a long-term treatment. Optimal administration route is intravenous or subcutaneous, not intramuscular. The administration of aspirin or other antiplatelet agents is forbidden.

Treatment of haemarthrosis

Therapeutic gestures necessary to achieve hemostasis are represented by immediate administration of GAH in cooperation with hematology, the initiation of analgesia (rest and / or immobilization, ice and rarely puncture aspiration) and after that, rehabilitation (early, under surveillance), all for prevent irreversible changes. Puncture and aspiration is controversial and is used only in limited circumstances because of the risk of the disease. The removal of intra-articular blood reduces pressure and develops a new intra-articular bleeding if adequate factorial plasma level was not reached or if hemostasis has occurred, is not possible aspiration of blood because it is already clotted. Puncture aspiration can be performed only if the plasma exceeded 20% and less than 12 hours after bleeding.

Treatment of synovitis

Non-surgical synovectomy (synoviorthesis). This term describes the intra-articular injection of a substance that will restore to normal a hypertrophied or inflamed synovia.

Chemical synovectomy (SC). SC with Rifampicin has a proteolytic effect producing fibrosis in the subsynovial venous plexus similar to pleurodesis with adriamycin. It is indicated in acute hemarthrosis.

Radioactive synovectomy (SR). The isotopes used are either Au198 or Itrium90. The procedure is relatively risky on an immature skeleton and can cause lesions of growth cartilage and chromosomal aberrations. Early complications include septic arthritis, local burns and irritation, and late complications such as chronic inflammation and the postradiation sarcoma.

Orthopedic treatment

In acute lesions (hemarthrosis):

- Substitution;
- Joint aspiration puncture (with or without immobilization), ice;
- Analgesia;
- Rehabilitation treatment under supervision;
- Walking without support;
- Reeducation pool.

In chronic arthropathy:

- Corrections of amplitude loss in functional positions, gradual mobilization with orthesis;
- Occupational therapy essential in all stages of arthropaty; it will allow the patient to return to independent living. It takes place in a specialized center. Adult patient will continue the exercises at home, as long as the young patients should be trained.

Surgical treatment

It has some historical objectives, which are saving life and saving limb.
Concentrates of factors VIII and IX make elective surgery feasible.
Cooperation between orthopedic surgeon and hematologist, complete and correct diagnosis, detecting the antifactor antibodies and viral status are essential.

Surgical Basic Principles

Staging of the procedures is required within this very demanding and rigorous surgery. Therefore, it will be performed multiple procedures during the same operation, a careful hemostasisis needed, the incision made is minimal, the procedure is made using electrocautery and is recommended to use a tourniquet, also utilization of local adjuvant measures (tranexamic acid, fibrin film). One should not use external fixation or percutaneous pins. Drainage is controversial, elastic compression and immobilization in plaster device can be used. In the cases operated in our Department (knee hemophilic arthropaties) we have used a postoperative autotransfusion device (CBS II).
Only subcutaneous injections are used, spinal anesthesia is not recommended.
GAH inhibitors increase the risk of complications.[6]
Given the high incidence among hemophiliac patients of hepatitis B or C, precautions from the operator and other personnel are recommended.

Indications-Contraindications

Indications

Chronic synovitis that cannot be controlled conservatively (synovectomy).
Limited range of motion: a) contractions of the soft tissues that cannot be corrected by conservative methods and b) deformed joints (correction

osteotomies), angular bone deformation requiring corrective osteotomies, degenerative joint changes requiring joint replacement, pseudotumor hemophilia and pain that accompanies all the above.

Contraindications
Acute Hepatitis
Inhibitors (antibodies antifactor VIII or IX)
HIV patients with CD4 counts below 200/mm3 level (risk of infection by 60%).

Synovectomy
A major procedure that will release the knee by removing a thick, hypertrophic, hyper vascular tissue, which releases toxic enzymes such as cathepsin D intra-articular, and is a source of repeated bleeding due to low resorption capacity and high friability .

Open synovectomy
Currently not used widely because it offers only a reduction in number of hemarthrosis and pain and does not improves joint range of motion, as well as it does not prevent further deterioration of the joint.

Arthroscopic synovectomy
The first experiences were reported by Kim and Wiedel in 1983. Indications are chronic hemophiliac synovitis persisting after 3 - 6 months and no response to conservative treatment, and as a secondary procedure after non-surgical synovectomy. It reduces pain and the number of hemarthrosis, sometimes offering discrete improving of mobility. It is a method with low risk and satisfactory results. The only disadvantage is relatively poor control of postoperative bleeding and the risk of additional hemarthrosis. It must be made as early as posible.[7] Arthroscopic synovectomy is not devoid of complications, on the topic today some controversy persists regarding indications. Consensus is achieved through the indication for decompression of the painful knee with chronic synovitis and/or in various stages of chronic arthropathy.
With the increasing use of arthroscopic synovectomy, one should reconsider his decision when choosing between this procedure, open synovectomy or non-surgical synovectomy (synoviorthesis).

Total knee arthroplasty
Indications they are the severe debilitating pain, reduced joint mobility, deformities, particularly with contracture in flexion and recurrent hemarthrosis. This technique presents a number of disadvantages, such as: the infection rate is seven times higher than routine knee arthroplasty, the risk of early mobilization of the implant, artroplasty failure and that patients are young and active. The results include a decrease or disappearance of pain, improving joint amplitude and correction of the deformities. The need for large bone resection to correct

deformities may require greater implant stability, using relatively small components, proximal axis of rotation and relative muscular atrophy with impaired functionality.[9]
It must be observed and corrected the ligamentar imbalance after the resection which is necessary to correct asymmetrical deformity. Sometimes the capsulotomy is needed to get full extension.
Postoperative knee extension must be maintained using an orthotics. If there is risk of vascular complications, knee flexion should be immediately put on. Passive drainage is used postoperatively for 24 - 48 hours. Continuous passive motion is started after removal of drain tubes. Support is authorized as soon as is borne by the patient.

Hip arthroplasty

In childhood, rapidly progressive hip arthropathy may result from a single hemarthrosis that increases intracapsular pressure that may lead to osteonecrosis of the femoral head. However, arthropathy of the hip is more often the consequence of chronic synovitis, like other arthropaties.
We should keep in mind the modifications that might occur in anatomy of the coxofemoral joint, narrowing of the medullar channel, with excessive anteversion and valgus of the femoral head and neck, accompanied by acetabular protrusion. Due to severe and excessive fibrosis, a muscle release may be needed. Also, bone stock is almost always of poor quality.
In patients with significant damage to the coxofemural joints, total hip arthroplasty was extremely efficient.
A unique aspect in hemophiliac patients is the limping because of the knee and ankle arthrofibrosys. This will produce high forces that act on the hip balance due to the lengthening of the lever arm and the loss of function as shock absorbers of the knee and ankle.
Part of the reason for the loosening of the prosthesis in hemophiliac can be due to the additional stress from the limping. Another consideration includes the possibility of bleeding in the membranes formed at bone-cement interface.
All these arguments will highlight the difficulty of this type of intervention and the necessity to perform this surgery in a center with experience in this field.[4]

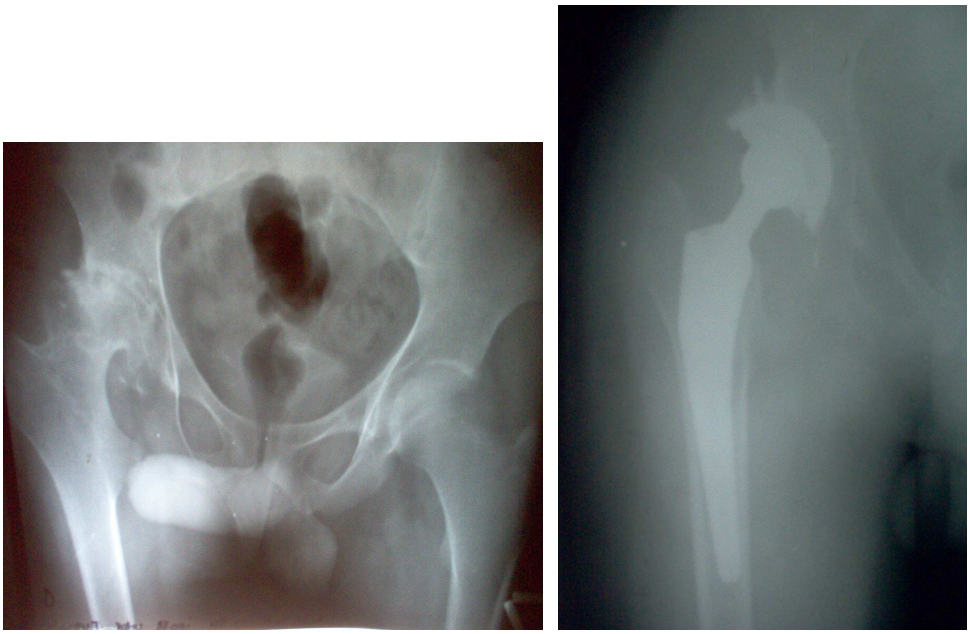

Figure 3. Chronic hemophilic arthropathy of the hip; total hip arthroplasty with uncemented prosthesis

Arthrodesis

Ankle, shoulder and elbow arthrodesis has been satisfactory on small series of patients with hemophilia. Using internal fixation at the expense of external transcutaneous fixation, is recommended because it reduces bleeding and infection around the pins. The fixed contracture in flexion can be corrected by removing the bone edges during arthrodesis. Gamble et al. recommended arthrodesis with compression of the ankle to relieve pain, reduce episodes of hemarthrosis and reduce equine position in arthropathic hemophilia in adults.

Material and method

We analyzed a group of 73 patients in the IInd Orthopedics Department in Timisoara, between 2003 and 2009. The age interval was 9 - 34 years (average 17,4 years).

It was performed 75 interventions. In this group we had HCV and HBV infections in 47 patients, osteoporosis and osteopenia in 52 patients. The patients came from all geographic regions of the country.

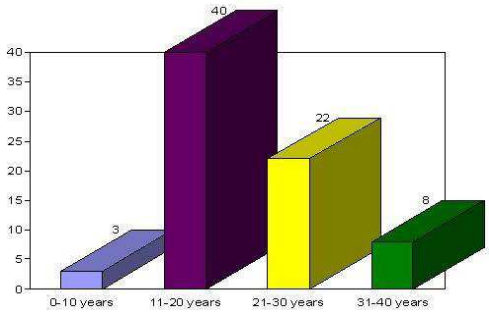

Chart 4. Distribution by age group

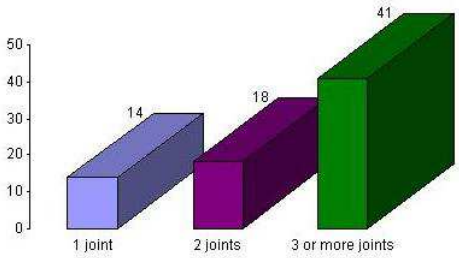

Chart 5. Distribution of joints affected by levels

Types of interventions performed in our group:

- elbow synovectomy 6;
- knee synovectomy 46;
- arthroscopic ankle synovectomy 3;
- total hip arthroplasty 2;
- radial head resection 4;
- knee arthrodesis 5;
- ankle arthrodesis 3;
- other interventions 4.

Pain when walking was estimated to severe by 4 patients and it remained moderate for the rest. Pain intensity was quantified using self-evaluation based on Visual Analogue Pain Scale (**Chart 6**).

1 The absence of pain score 0 but that does not disturb
2 Moderate, tolerated without medication
3 severe but doesn't affect socially and professionally
4-5 more severe affect socially and professionally
6 Severe
7-9 Very severe
10 most severe, suicidal tendencies

Chart 6. Visual Analogue Pain Scale

Surgery was indicated in case of debilitating pain and marked reduction of the range of motion, joint swelling and vicious positions of limbs with or without recurrent hemarthrosis.

General contraindications consisted of:

- High concentration of inhibitors (antibodies to factor VIII, IX),
- Hepatitis.

Preoperative evaluation of patients consisted of a series of laboratory investigations and imaging:

- Concentration of the deficit factor,
- Viral status,
- Presence of inhibitors,
- Radiographs of the anterior-posterior, lateral and axial,
- MRI,
- Osteoporosis confirmed by osteodensitometry.

Osteoporosis or osteopenia was present in all patients. They were found in the cases where radiological images were not pathologically significant. Preoperative investigations used in our group included triple X-ray incidence anterior - posterior, lateral and axial profile in flexion of 45 for the knee, anterior - posterior and profile in flexion and maximum extension for elbow, front and profile for the ankle, front and Schneider incidence for the hip.

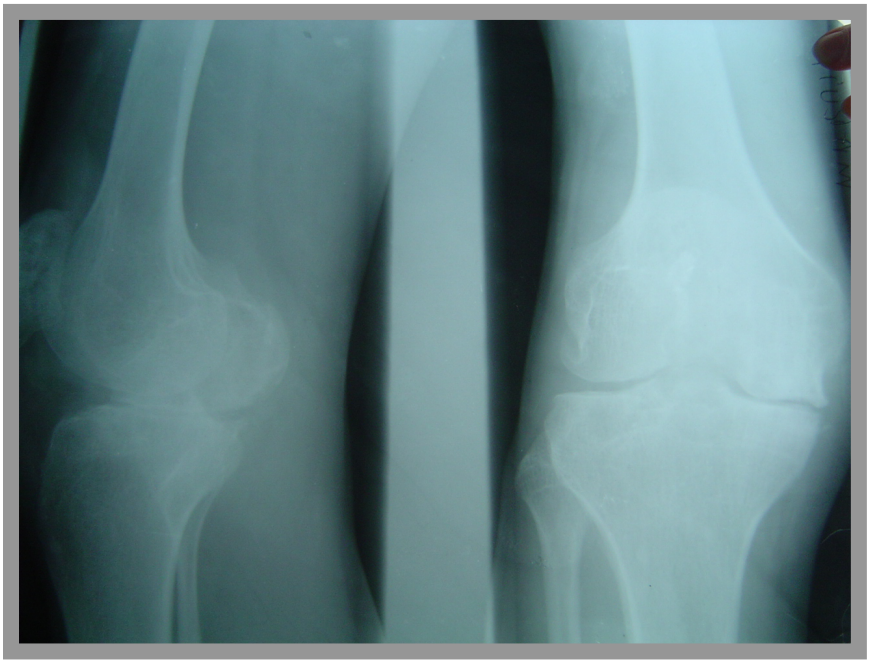

Figure 5. Artopathy chronic knee haemophilia

Type of interventions performed in the knee and hip:
- Synovectomy (arthroscopy),
- Debridment (arthroscopy, open),
- Arthroplasty,
- Arthrodesis.

During these interventions, we had to face a series of difficulties, referring to:
- Increased deformities,
- Difficult arthroscopic access due to arthrofibrosis,
- Synovial hypertrophy,
- Arthrofibrosis
- Bone cuts tend to bleed a lot, requiring 100% substitution,
- Poor soft tissue coverage, severe muscle atrophy,
- Poor bone stock.

Type of interventions performed in the elbow and ankle
- Elbow
  - Sinovectomie open with radial head excision,
    - contraindicated in children.
- ankle and subtalar joint
  - Arthroscopic synovectomy,
  - Arthrodesis.

Difficulties related to elbow and ankle surgery:
- Synovial fragility requiring synovectomy with the shaver,
- Resection of radial head - just below the ulnar facet (to preserve the anular ligament),
- Mobilization elbow - early, without force maneuver,
- Difficult access in case of ankle arthroscopy.

Discussion

Clinical forms of musculoskeletal manifestations of haemophilia can be divided into 3 groups as follows:

Group I. Includes typical manifestations of haemophilia, only present in this disease, such as haemophilic pseudotumor. They need a special and unique treatment.

Group II. Includes manifestations such as severe arthrosis and chronic synovitis, which may also be consequence to other causes outside of haemophilia. The early treatment may be similar, but severe forms require an experienced and dedicated approach.

Group III. These events are very similar with non haemophilic pathology, such as early stages of arthropaties, synovitis and intermittent haemarthrosis. Simple and pathological fractures can also be affiliated with this group. Treatment generally is

not specific; it will join the rules and general principles of treatment of haemophilic patients.

Patients in Group I must always be advised and treated in a specialized orthopedic center for haemophiliac patients, with a nurse with experience and additional staff (especially anesthesiologist) and in close cooperation with the department of hematology. It is also recommend that all elective surgery to be performed in such centers, including those in group II.

Surgical treatment of patients in group II in the early stages and with a proper substitution is not different from that of non haemophilic patients. In case of arthropathy with severe deformities and skeletal defects, we must be prepared for specific and non-standard implants.

Patients in Group III, particularly those with trauma or acute hemarthrosis should be treated immediately in any hospital with a department of hematology and sent to a specialized center only after solving the acute situation. All patients requiring conservative treatment may be affiliated with this group. We should keep in mind that the first step in the treatment of any musculoskeletal complications of hemophilia is the administration of GAH as soon as possible and that any surgical procedure is possible only after total substitute treatment by hematologists.

Without treatment haemophilic patients will die in childhood or as young adults and will suffer from musculoskeletal or other problems. However, in theory, with an ideal substitution and no episodes of bleeding, these patients may be considered completely healthy and without any disability [2]. This depends on many factors, but especially the economic situation of the health system and the patient as well. Substitutive treatment depends entirely of hematologist and the patient's discipline.

We must be prepared to treat patients with any form of hemophilia. The severity of the manifestations will depend on the severity of the disease and the quality of treatment. The treatment for hemophilia requires a multidisciplinary approach and is very expensive.

Coagulopathy is associated with a high trauma burden and, as such, is often associated with increased mortality.[3]

Conclusions

Bleeding complications may be avoided by an expert haematological control.

Arthroscopic synovectomy may be indicated in moderate stages of hemophilic artropathy of knee and ankle.

Arthroscopic procedures can be performed safely in patients with low concentrations of inhibitors.

Open synovectomy of the elbow on minimum approach with radial head resection has given excellent results.

Knee arthrodesis remains a solution for haemophilic patients with severe joint deformities.

Arthroplasty is indicated even at young ages.

With substitute treatment and a correct surgical indication, surgery in haemophilic patients can be performed with acceptable risk and good results.

R E F E R E N C E S

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